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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/526,697	05/05/2005	Mark E. Dudley	233876	9619

45733 7590 12/17/2008

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EXAMINER	
BELYAVSKYI, MICHAIL A	

ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
12/17/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/526,697	DUDLEY ET AL.	
	Examiner	Art Unit	
	Michail A. Belyavskyi	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 October 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *1-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1 Claims 1-40 are pending.

Claims 1-22 stand withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

2. Claims 23-40 read on a method of promoting the regression of a cancer in a mammal comprising administering nonmyeloablative lymphodepleting chemotherapy and subsequently administering autologous T-cells , which have been previously isolated and stimulated in vitro with the antigen of the cancer of are under consideration in the instant application.

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 23- 35,37 and 38 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Dudley et al (J of Immunology, May 2001, Vol. 24, IDS) or WO'9705239 in view of US Patent 6,447,767 (IDS) and Riddell et al. and US Patent 5,126,132 for the same reasons set forth in the previous Office Action, mailed on 08/06/08.

Applicant's arguments, 10/17/08 have been fully considered, but have not been found convincing.

Applicant asserts that according to Declaration under 1.132 by DR. Dudley(i) administering nonmyeloablative lymphodepleting chemotherapy and subsequently administering autologous T cells, which have undergone one cycle of rapid expansion provides unexpectedly superior clinical responses in patients as compared to the methods in which patients were not administered nonmyeloablative treatment and in which the T-cell has undergone multiple cycle of rapid expansion, (ii) based on the results in Dudley 2001 and Yee, one of ordinary skill in the art at the time the invention was made would not expect that T cells that had undergone only one cycle of rapid expansion, would result in a positive objective clinical response.

Contrary to Applicants assertion, it is noted that the that the instant rejection is under 35 USC103 and that unobviousness cannot be established by attacking the references individually when the rejection is based on the combination of the references. see In re Keller, 642 F.2d 4B, 208 USPQ 871, 882 (CCPA 1981) See MPEP 2145. This applicant has not done, but rather argues the references individually and not their combination. One cannot show non-obviousness by attacking references individually where the rejections are based on a combination of references. In re Young 403 F.2d 759, 150 USPQ 725 (CCPA 1968).

Moreover, it has been recently stated that KSR forecloses the argument that a specific teaching, suggestion, or motivation are required to support a finding of obviousness See Board decision (see *KSR International Co v Teleflex Inc*., 550U.S.-, 82 USPQ2d 1385, 2007).

It is well settled that a conclusion of obviousness does not require absolute predictability, only a reasonable expectation of success In re O'Farrell, 853 F2d 894,903-04,7 USPQ2d 1673,1681 (Fed.Cir.1988) and In re Longi, 759 F2d 887,225 USPQ2d 645, 652 (Fed.Cir.1985)

The motivation need not be found in the references sought to be combined, but may be found in any number of sources, including common knowledge, the prior art as a whole, or the nature of the problem itself. In re Dembiczak, 175 F.3d 994, 999 (Fed. Cir. 1999).
As explained in Motorola, Inc. v. Interdigital Tech. Corp., 121 F.3d 1461, 1472 (Fed. Cir. 1997), "there is no requirement that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art."

In the instant case, Dudley et al., teach a method of promoting the regression of melanoma in a mammal which comprising administering an autologous T cell which have been previously isolated, selected for highly avid recognition of melanoma antigen and expanded in vitro (see entire document, Abstract and page 364 in particular). Dudley et al teach that to same patient IL-2 at various dosages (125,000 IU/kg -and 720,000IU/kg) was administered subsequently to autologous T cells (see Material and methods in particular). Dudley et al teach that some patien had also received the MART-1 peptide (see page 364 in particular). Dudley et al. teach that to overcome the poor persistence of adoptive transferred of T cells several variation on patient treatment protocol could be considered, including lymphodepleting chemotherapy. Dudley et al. teach that said treatment might improve lymphocyte survival and treatment efficacy.

WO' 239 teaches a method of promoting the regression of cancer in a mammal compring administering to mammal an autologous T-cells which have been stimulated *in vitro* with antigen of the cancer (see entire document, Abstract and pages 12, 17, 22, 48 and 49 in particular). WO' 239 teaches the administration of IL-2 to the same patients at various concentrations (see pages 16 and 18 in particular)

The claimed invention differs from the reference teaching in that the Dudley et al., or WO' 239 does not explicitly teach a patient treatment protocol comprising administering non-myeloablative lymphodepleting chemotherapy comprising administration of cyclophosphamide and fludarabine prior to administering an autologous T cell which have been previously isolated, selected for highly avid recognition of melanoma antigen and expanded in vitro and wherein said T cells which have been previously isolated and stimulated *in vitro* with the antigen of the cancer have been further subjected to one cycle of rapid expansion using irradiated allogeneic feeder cells, OKT3 antibody and IL-2 .

US Patent '767 teaches a method of treating cancer patient, including melanoma, comprising administering to the patient non-myeloablative treatment, including administering cyclophosphamide and fludarabine prior of administering hematopoietic cells (see entire document, Abstract, columns 3, 4 , 8 and 9 in particular). US Patent '767 teaches that said non-myeloablative treatment should be used to overcome the poor persistence of adoptive transferred of T cells. Moreover, US '767 teaches that administering hematopoietic cells might contains T cells, since depletion T cell of donor stem cell has been know to increase the risk of graft rejection (see column 12 and 16 in particular). Thus, the examiner disagrees with applicant's statement, that " US Patent 767 only teaches administering non-myeloablative theraphy prior to the administering hematopoietic stem cells , not T –cells" However, it is noted that said statement is irrelevant for the instant rejection since US Patent'767 has been used as a secondary reference to show that at the time the invention was made one skill in the art would know that administering to the mammal nonmyeloablative lymphodepleting chemotherapy was a routinely used method to induced donor specific tolerance in a method of treating cancer patient, including melanoma.

US Patent' 132 teaches a method of treating cancer, including melanoma, comprising administering to the patient an effective amount of autologous tumor infiltrating lymphocytes (see entire document, Abstract in particular). Us Patent'132 teaches a general methodology how to determine an effective amount of said cells and also teaches that the preferred amount is from about $5x\ 10^9$ to $5x\ 10^{11}$ cells.

Riddell et al., teach a method of *iv vitro* growing and expanding a large number of antigen specific T cells comprising rapid expansion using irradiated allogeneic feeder cells, OKT3 antibody and IL-2. The Examiner disagrees with Applicant's interpretation of Riddell et al., teaching. Riddell et al., teach an alternative culture method to clone and propagate human T cells that permitted retention of Ag specificity but did not require restimulation with Ag. Said expanded antigen-specific T cells would be useful for adoptive immunotherapy. However, nowhere do Riddell et al., teach that multiple rounds of rapid expansion should be used for adoptive immunotherapy. Moreover, it is noted that said reference has been used as the secondary reference to show that at the time the invention was made one skill in the art would know how to expand antigen specific T cells using irradiated allogeneic feeder cells, OKT3 antibody and IL-2.

It is the examiner position that it would be conventional and within the skill of the art to determine the effective amount of administered expanded antigen specific T cell for adoptive immunotherapy.

All the claimed elements were known in the prior art and one skill in the art could have combine the elements as claimed by known methods with no change in their respective function and the combination would have yield predictable results to one of ordinary skill in the art at the time of the invention (see *KSR International Co v Teleflex Inc*., 550U.S.-, 82 USPQ2d 1385, 2007).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of US Patent '767, US Patent '132 and Riddell et al., to those of Dudley et al., or WO'239 to obtain a claimed method of promoting the regression of cancer in a mammal comprising administering non-myeloablative lymphodepleting chemotherapy comprising administration of cyclophosphamide and fludarabine prior to administering an autologous T cell which have been previously isolated, selected for highly avid recognition of melanoma antigen and expanded in vitro.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, because to overcome the poor persistence of adoptive transferred of T cells several variation on patient treatment protocol could be considered, including non-myeloablative treatment, including administering cyclophosphamide and fludarabine prior of administering T cells as taught by US Patent '767 that can be used in combination with by the method taught by Dudley et al. or WO'239. The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Semaker. 217 USPQ 1, 5 - 6 (Fed. Cir. 1983). See MPEP 2144.

Claims 26 –34 are included because it would be conventional and within the skill of the art to : (i) determine the optimal duration and dosage of administering cyclophosphamide and fludarabine; or (ii) optimal amount of administered T cells. Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A.

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at

the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

With regards to Applicant's statement of unexpected results.

The issue is whether the properties differ to such an extent that the difference is really surprising. These effects are not surprising because as has been discussed supra, at the time the invention was made one skill in the art would know that administering to the mammal nonmyeloablative lymphodepleting chemotherapy was a routinely used method to induced donor specific tolerance in a method of treating cancer patient, including melanoma. Thus, one skill in the art would expect that administering nonmyeloablative lymphodepleting chemotherapy prior of administering autologous T cells would provide better clinical responses in patients as compared to the method in which patients were not administering nonmyeloablative treatment.

5. Claims 36, 39 and 40 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Dudley et al (J of Immunology, May 2001, Vol. 24, IDS) or WO'9705239 in view of US Patent 6,447,767 (IDS), Us Patent 5,126,132 and Riddel et al., as applied to claims 23- 35, 37 and 38 above, and further in view of Kawakami et al (PNAS, 1994, V.91, pages 6458-6462) and Stevens et al (J. of Immunology, 1995, 154, pages 762-771) for the same reasons set forth in the previous Office Action, mailed on 08/06/08.

Applicant's arguments, 10/17/08 have been fully considered, but have not been found convincing.

Applicant asserts that because the claimed method produces unexpectedly superior clinical responses as compared to the method of Dudley 2001 or WO'239, the obviousness rejection cannot be maintained.

As has been discussed supra, it is the Examiner position that combination therapy, wherein nonmyeloablative chemotherapy has been administered prior of administering autologous T cells was not surprising and was expected to provide better clinical responses in a patient than when autologous T cells has been administered without nonmyeloablative chemotherapy.

The teaching of Dudley et al., WO' 239, US Patent '132 and US Patent'767 and Riddell et al., have been discussed, supra.

Dudley et al., WO' 625 and US Patent '767 and Riddel et al., do not explicitly teach a method of promoting the regression of a cancer in a mammalian wherein antigen of cancer consists of

amino acids 26-35 of MART-1 or amino acids 209-217 of gp100, as claimed in claims 36, 39 and 40.

Kawakami et al., teach melanoma differentiated antigens gp100 that is frequently observed as a targets of tumor infiltrating lymphocytes (see entire document, Abstract in particular). Kawakami et al., teach that peptides consisting amino acids 209-217 of gp100 has been used for in-vitro sensitization of T cells (see Materials and Methods in particular). Kawakami et al., teaches that incubation of T cells with said antigens consistently increase reactivity of T cells towards said immunodominant epitope. Obtaining said melanoma-specific T cells would be beneficiary for treating and promoting regression of melanoma in patients

Stevens et al., teach melanoma differentiated antigens MART-1 that is frequently observed as a targets of tumor infiltrating lymphocytes (see entire document, Abstract in particular). Stevens et al., teach that peptides consisting of amino acids 25-35 of MART-1 has been used for in-vitro sensitization of T cells (see Materials and Methods in particular). Stevens et al., teach that incubation of T cells with said antigens consistently increase reactivity of T cells towards said immunodominant epitope. Obtaining said melanoma-specific T cells would be beneficiary for treating and promoting regression of melanoma in patients

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of Kawakami et al., and Stevens et al., to those of Dudley et al., WO' 625 and US Patent '767 to obtain a claimed a method of promoting the regression of a cancer in a mammalian wherein antigen of cancer consists of amino acids 26-35 of MART-1 or amino acids 209-217 of gp100.

Specific statements in the references themselves which would spell out the claimed invention are not necessary to show obviousness, since questions of obviousness involves not only what references expressly teach, but what they would collectively suggest to one of ordinary skill in the art. See CTS Com. v. Electro Materials Corp. of America 202 USPQ 22 (DC SINY); and In re Burckel 201 USPQ 67 (CCPA).

All the claimed elements were known in the prior art and one skill in the art could have combine the elements as claimed by known methods with no change in their respective function and the combination would have yield predictable results to one of ordinary skill in the art at the time of the invention (see *KSR International Co v Teleflex Inc.*, 550U.S.-, 82 USPQ2d 1385, 2007).

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

6. No claim is allowed.

7. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is 571/ 272-0840 The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on 571/ 272-0878.
The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Michail A Belyavskyi/
Primary Examiner, Art Unit 1644